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REVIEW

Ovarian cancer: new strategies and emerging targets for the treatment of patients with advanced disease

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ABSTRACT

Recently approved therapies have contributed to a significant progress in the management of ovarian cancer; yet, more options are needed to further improve outcomes in patients with advanced disease. Here we review the rationale and ongoing clinical trials of novel combination strategies involving chemotherapy, poly ADP ribose polymerase, programmed death 1 (PD-1)/PD-ligand 1 immune checkpoint and/or vascular endothelial growth factor receptor inhibitors. Further, we discuss novel agents aimed at targets associated with ovarian cancer growth or progression that are emerging as potential new treatment approaches. Among them, agents targeted to folate receptor α, tissue factor, and protein kinase-mediated pathways (WEE1 kinase, phosphatidylinositol-3 kinase α, cell cycle checkpoint kinase 1/2, ATR kinase) are currently in clinical development as mono- or combination therapies. If successful, findings from these extensive development efforts may further transform treatment of patients with advanced ovarian cancer.

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I. Introduction

Although incidence rates of ovarian cancer have been decreasing by about 1–2% each year, ~21,750 new cases are expected in the United States in 2020, with a diagnosis of epithelial ovarian cancer in ~90% of these patients.[1,2] Primary peritoneal and fallopian tube cancers may be referred to as part of this group of malignancies. The adoption of more effective treatment options with novel chemotherapeutic regimens and targeted agents has significantly contributed to the improvements in patient outcomes observed in the past decade (Figure 1).[1–4]

Nonetheless, a substantial proportion of patients with ovarian cancer are primarily resistant to treatment with available agents or develop secondary resistance over time, with disease progression and a poorer prognosis. In 2020, ~13,940 deaths are estimated to occur in the United States due to ovarian cancer. The current, overall 5-year survival rate is 48% and only 29% in the most advanced disease stages.[2] This limited survival underscores the need of identifying additional safe and effective treatments to improve outcomes in patients with ovarian cancer, particularly in advanced stage disease. The development of novel agents or regimens with improved tolerability may also contribute to provide treatment options associated with a better health-related quality of life for this patient population.

In this review, we discuss new strategies that are emerging for the treatment of patients with advanced ovarian cancer across a broad range of mechanisms of action, outlining the rationale underlying the selection of new targets in ovarian cancer and the novel combination approaches currently being evaluated in clinical trials.

II. Angiogenesis, genomic instability, and the immune microenvironment in ovarian cancer

Angiogenesis and vascular endothelial growth factor receptor (VEGFR) inhibition

Multiple lines of evidence have demonstrated that angiogenesis may play a key role in the survival and progression of various tumor types, including advanced ovarian cancers.[5] Once released within the tumor microenvironment, proangiogenic growth factors such as VEGF can induce activation and proliferation of vascular endothelial cells, promote tumor-associated angiogenesis and contribute to the survival of endothelial cells in the newly formed vessels. In addition, proangiogenic factors modify the vascular tone and increase vascular permeability thereby contributing to further support the growth and survival of tumor cells.[5]

In ovarian cancer, overexpression of VEGF leads to an increase in tumor microvessel density, which has been found to be associated with disease progression and worse prognosis.[5] Consistently, VEGF inhibition by bevacizumab in combination with chemotherapy, followed by maintenance therapy, has proven effective in delaying disease progression in ovarian cancer when administered after initial surgical resection or in recurrent platinum-sensitive disease, and as monotherapy or combined with chemotherapy in patients with platinum-resistant disease.[6–8]

However, various mechanisms may allow escape of tumor cells from therapeutic control, including selection of tumor clones with increased expression of compensatory signaling pathways or clones with an increased capacity to grow and invade normal tissues in conditions of limited angiogenic support.[9,10] Multiple

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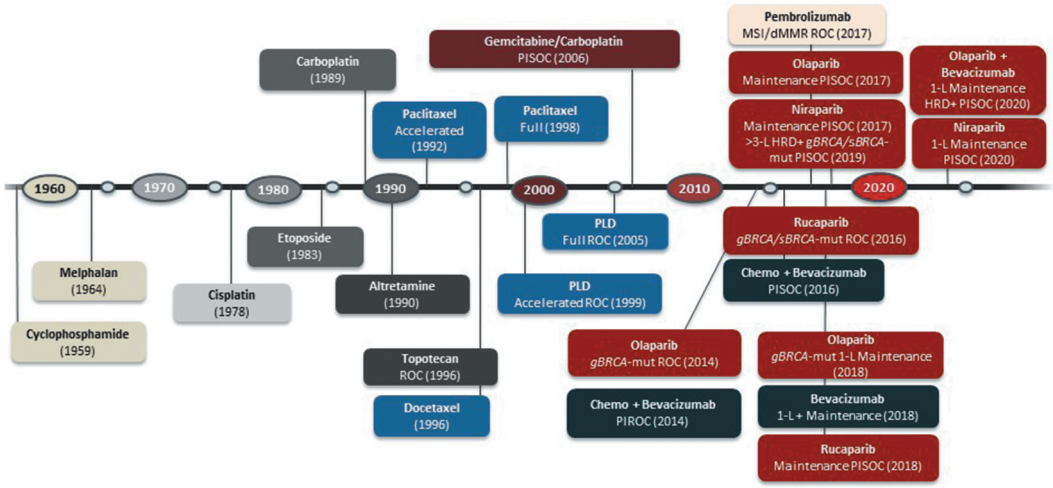

Figure 1. FDA-approved drugs in advanced ovarian cancer. dMMR: deficient mismatch repair, FDA: US Food and Drug Administration, HRD: homologous recombination deficiency, L: line of treatment, MSI: microsatellite instability high, mut: mutated, PISOC: platinum-sensitive ovarian cancer, PIROC: platinum-resistant ovarian cancer, PLD: pegylated liposomal doxorubicin.

approaches are thus being investigated to further improve clinical outcomes, through the development and characterization of novel antiangiogenic agents, and their use in combination regimens with agents targeting other key pathways in tumor cells (i.e. DNA repair) or immune checkpoints (i.e. programmed death rece ptor 1 [PD1]/PD-ligand 1 [PD-L1]).[11] Both VEGF receptor (VEG FR) 1 and 2 are expressed by microvascular endothelial cells in malignant ovarian tumors and borderline lesions suggesting their potential usefulness as targets for new therapeutic approaches.[5,12]

Nintedanib is a triple angiokinase inhibitor of the VEGFR, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR).[13] Combined treatment with this small-molecule inhibitor and chemotherapy (carboplatin/paclitaxel) in the AGO-OVAR12 phase III trial showed activity in patients with newly diagnosed, advanced ovarian cancer, with an improvement in median progression-free survival (mPFS) versus chemotherapy. However, treatment was associated with limited tolerability and a higher incidence of gastrointestinal adver se events (AEs) compared with the control group.[13]

Targeted inhibition of VEGFR2 with the small-molecule, tyrosine kinase inhibitor apatinib has demonstrated activity in advanced gastric cancer and other malignancies. Single-agent administration in an initial phase I study induced responses, although of limited duration, in patients with recurrent, platinum-resistant ovarian cancer.[14] Treatment with apatinib was most frequently associated with hand-foot syndrome, hypertension, nausea, and vomiting. Further evaluation is ongoing in combination with the DNA topoisomerase II inhibitor etoposide or the anti-PD-1 antibody camrelizumab in patients with advanced, platinum-resistant disease.[14]

In addition to VEGFR targeting, selective inhibition of angiopoietin binding to the Tie2 tyrosine kinase receptor may result in impairment of tumor-associated angiogenesis.[15] Investigation of combination treatment with the angiopoietin inhibitor trebananib (AMG386) plus paclitaxel showed a significant prolongation in mPFS versus paclitaxel alone in patients with recurrent disease (platinum-free interval <12 months), in the randomized phase III TRINOVA-1 trial. Edema (of any grade) was reported in more than half of patients receiving combination treatment, but most of the AEs usually related to VEGF-targeted therapy (i.e. hypertension, proteinuria, thrombotic events, wound-healing complications, gastrointestinal perforation) were infrequently observed.[15] At final analysis of this study, OS was significantly prolonged only in the patient subset with baseline ascites.[16] Combination treatment with trebananib plus pegylated liposomal doxorubicin in patients with recurrent, partially platinum-sensitive or resistant ovarian cancer (platinum-free interval ≤12 months, ENGOT-ov6/TRINOVA-2 phase III trial) dem onstrated an improvement in objective response rate (ORR), but not in mPFS, versus chemotherapy alone.[17] Recent findings from the randomized ENGOT-ov2/TRINOVA-3/GOG-3001 phase III trial of trebananib plus carboplatin/paclitaxel as first-line trea tment for advanced disease followed by maintenance with trebananib or placebo, showed no significant improvement in mP FS, the primary endpoint, compared with chemotherapy.[18] A phase Ib study is currently evaluating trebananib in combinati on with the PD-1 immune checkpoint inhibitor pembrolizumab in patients with advanced, platinum-resistant ovarian cancer.

Genomic instability and poly ADP ribose polymerase (PARP) inhibition

As in other tumor types, genomic instability may arise in ovarian cancer from the genetic abnormalities associated with malignant transformation, which often affects genes encoding homologous recombination (HR) DNA repair factors such as BRCA1 and BRCA2.[19–21] The PARP1 and PARP2 nuclear enzymes mediate repair of single-stranded (ss) DNA breaks, induced by ultraviolet light, radiation, chemotherapy, and other DNA-damaging agents, by base-excision repair.[22,23] In patients with germline or somatic defects in genes involved in HR repair (i.e. *BRCA1, BRCA2*), who cannot repair (ds) DNA breaks, inhibition of PARP activity blocks DNA repair and induces cell death.[22,23] Inhibition of PARP becomes synthetically lethal in the context of an inactivating *BRCA* mutation,

because HR defects make *BRCA*-mutated tumors 'addicted to' (dependent on) other DNA repair pathways.[24] Although PARP inhibitors were first shown to be effective in *BRCA*-mutated tumors, responses and clinical benefit have been observed in the presence of wild-type *BRCA1* or *2* genes, suggesting that other factors and genetic mutations, involved in HR DNA repair, may confer sensitivity to PARP inhibitors.[19,25,26] Beyond *BRCA*, genes encoding proteins involved in HR repair that may be mutated and associated with HR deficiency (HRD) in ovarian cancer include the Fanconi anemia genes *RAD51C, RAD51D, RAD50, BRIP1, BARD1, MRE11A*, and *PALB2* as well as the DNA mismatch repair genes *MLH1, MSH2, MSH6*, and *PMS2*.[27] In patients with ovarian cancer, germline mutations in HR genes have been identified more frequently than somatic tumor mutations (<10% of cases).[28]

Findings from multiple trials have demonstrated that PARP inhibition is an effective therapeutic strategy in ovarian cancer (Table 1). Treatment with single-agent rucaparib or olaparib is standard of care for patients with recurrent, platinum-sensitive or platinum-resistant *BRCA*-mutated disease, after 2 or 3 prior lines of chemotherapy, respectively.[4,25,26,29] In addition, the QUADRA study has shown efficacy of niraparib monotherapy in patients with HRD, including *BRCA*-mutated and non-mutated, recurrent ovarian cancer after four or more lines of chemotherapy (ORR, 28%).[30] These results supported the approval of niraparib by the Food and Drug Administration (FDA) for heavily pretreated patients with HRD+ disease.

Based on the results of the SOLO2, study 19, NOVA, and ARIEL 3 studies, olaparib, niraparib, and rucaparib are indicated for the maintenance treatment of patients with recurrent ovarian cancer who are in complete or partial response following prior platinum-based therapy, independent of their biomarker status.[4,25,26,29] Results from the randomized phase III SOLO1 trial have demonstrated that maintenance treatment with a PARP inhibitor is effective in newly diagnosed patients following first-line platinum-based chemotherapy.[31] Based on the extent of benefit observed, olaparib was approved by the FDA for clinical use in this indication for patients with *BRCA*-mutated tumors. Furthermore, the phase III studies ENGOT-OV26/PRIMA, VELIA, and PAOLA-1 have shown that both niraparib and veliparib, and the combination of olaparib plus bevacizumab are effective as first-line maintenance therapy in patients with advanced ovarian cancer, following response to prior platinum-based chemotherapy. Detailed study results are presented in Table 2 for the intent-to-treat populations and the subgroups analyzed (i.e. HRD+, *BRCA*-mutation+ patients). Although all three trials were positive in the intention-to-treat population, which included 'all-comers' despite specific genetic abnormalities, the patients that derived most benefit were HRD+, either due to a *BRCA* mutation or other HR defect.[32–35]

Nonetheless, ovarian tumors may display primary or secondary resistance to treatment with PARP inhibitors, prompting an extensive evaluation of biomarkers that may help to determine the underlying resistance mechanisms and contribute to the identification and selection of therapies/combination regimens, timing, and sequencing of treatments suitable for each patient.[36–41] Secondary mutations have been detected in patients with acquired resistance to PARP inhibitor therapy, including somatic mutations that restore *BRCA1/2* gene functions, through elimination of the open reading frame shift or by reverse mutation within the coding region.[37,41–43] Analysis of baseline and on treatment samples showed that the presence of heterogeneous *BRCA2* reversion mutations was associated with resistance to PARP inhibition in prostate and ovarian cancers.[42,43] In one of these studies, *BRCA* reversion mutations were detected in pretreatment samples in 18% of platinum-refractory *v* 2% of platinum-sensitive, high-grade ovarian carcinomas (p = .049). Patients without *BRCA* reversion mutations at baseline had significantly longer PFS following treatment with rucaparib compared with patients who had *BRCA* reversion mutations (median PFS, 9.0 *v* 1.8 months; HR, 0.12; p < .0001).[43] Additionally, heterogeneous mutations were identified in some patients after PARP inhibitor therapy.[43]

Primary and acquired resistance to PARP inhibition in patients with high-grade ovarian cancers were also found associated with secondary, somatic mutations, including a truncation mutation,

Table 1. Pivotal trials and FDA approvals of PARP and VEGF inhibitors in advanced ovarian cancer.

Drug	Maintenance	Later-Line Treatment	FDA Approval
Olaparib[a]	SOLO-2 (*BRCA*-mutated) Study 19 *(Aug 17, 2017)* SOLO-1 (*BRCA*-mutated) *(Dec 19, 2018)* PAOLA-1 (HRD-positive) *(May 8, 2020)*	Study 42 (*BRCA*-mutated) *(Dec 19, 2014)*	> 3rd line, germline *BRCA*, treatment *(Dec 19, 2014)* > 2nd line, no biomarker, maintenance after response to platinum *(Aug 17, 2017)* Front-line, germline and somatic *BRCA*, maintenance after response to platinum *(Dec 19, 2018)* Front-line olaparib plus bevacizumab, HRD-positive, maintenance after response to platinum *(May 8, 2020)*
Niraparib[b]	NOVA *(Mar 27, 2017)* ENGOT-OV26/PRIMA *(April 29, 2020)*	QUADRA *(Oct 23, 2019)*	2nd line, no biomarker, maintenance after response to platinum *(March 27, 2017)* >3rd line, HRD+, germline and somatic *BRCA*, platinum-sensitive, treatment *(Oct 23, 2019)* Front-line maintenance after response to platinum (*April 29*, 2020)
Rucaparib[c]	ARIEL3 *(April 6, 2018)*	Study 10 (*BRCA*-mutated) ARIEL2 (*BRCA*-mutated) *(Dec 19, 2016)*	> 2nd line, germline and somatic *BRCA*, treatment *(Dec 19, 2016)* > 2nd line, no biomarker, maintenance after response to platinum *(Apr 6, 2018)*
Bevacizumab[d]	GOG218 *(June 13, 2018)* OCEANS – GOG213 *(Dec 6, 2016)*	AURELIA *(Nov 14, 2014)*	1st and later-line treatment plus maintenance *(Nov 14, 2014; Dec 6, 2016; June 13, 2018)*

[a]Olaparib Prescribing Information. AstraZeneca Pharmaceuticals LP, May 2020; [b]Niraparib Prescribing Information. Tesaro Inc., April 2020; [c]Rucaparib Prescribing Information. Clovis Oncology Inc., May 2020; [d]Bevacizumab Prescribing Information. Genentech/Roche, May 2020.

FDA: US Food and Drug Administration, HRD: homologous recombination deficiency, PARP: poly ADP ribose polymerase, VEGF: vascular endothelial growth factor.

Table 2. Pivotal trial results for front-line maintenance therapy in patients with newly diagnosed, advanced ovarian cancer after response to platinum-based therapy.

Drug/Regimen	Phase III Trial	Patient Population	N	Outcomes	Reference
Niraparib vs placebo	ENGOT-OV26 /PRIMA	ITT	733	mPFS, 13.8 *v* 8.2 mo, HR 0.62, $p < .001$; mOS at 24 mo, 84% *v* 77%, HR 0.70	Gonzalez-Martin et al., 2019
		HRD+ (including *BRCA*-mt+)	373	mPFS, 21.9 *v* 10.4 mo, HR 0.43, $p < .001$	
Veliparib vs placebo	VELIA	ITT	1140	mPFS, 23.5 *v* 17.3 mo, HR 0.68, $p < .001$	Coleman et al., 2019
		HRD+ (including *BRCA*-mt+)	421	mPFS, 31.9 *v* 20.5 mo, HR 0.57, $p < .001$	
		BRCA-mt+	200	mPFS, 34.7 *v* 22.0 mo, HR 0.44, $p < .001$	
Olaparib plus bev vs placebo plus bev	PAOLA-1	ITT	806	mPFS, 22.1 *v* 16.6 mo, HR 0.59, $p < .001$	Ray-Coquard et al., 2019
		HRD+ (including BRCA-mt+)	387	mPFS, 37.2 *v* 17.7 mo, HR 0.33	
		HRD+ (not including *BRCA*-mt+)	150	mPFS, 28.1 *v* 16.6 mo, HR 0.43	
		BRCA-mt+	237	mPFS, 37.2 *v* 21.7 mo, HR 0.31	
		HRD-negative	277	mPFS, 16.6 *v* 16.2 mo, HR 1.00	

Bev: bevacizumab, HRD: homologous recombination deficiency, HR: hazard ratio, ITT: intent to treat, mo: month, mOS: median overall survival, mPFS: median progression-free survival.

in the genes *RAD51C* and *RAD51D*, which encode proteins involved in (ds) DNA break repair by HR.[44] Complementation assays confirmed the association between the presence of these mutations and resistance to PARP inhibition therapy.[44] Combination with other targeted inhibitors as well as earlier administration of a PARP inhibitor in the course of the disease may help to decrease or delay the development of resistance in ovarian cancer, and thus improve treatment outcomes for patients with advanced disease.[25,44]

The immune microenvironment, activity of PD-1/PD-L1-targeted immune checkpoint inhibitors and other immunotherapeutic approaches

The tumor immune microenvironment in ovarian cancers is quite complex with infiltration by helper or effector T cells and antigen-presenting cells (i.e. dendritic cells), production of interferon (INF) γ, interleukin (IL) 2 and IL-16 (a chemoattractant), which may result in antitumor immune responses. Conversely, the activity of VEGF and other 'pro-tumor' immune factors such as transforming growth factor (TGF) β, PD-L1, tumor necrosis (TNF) α, IL-6, and IL-10 often contribute to tumor survival and escape from immune control.[45–48]

Overexpression of VEGF may induce downregulation of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion-molecule-1 (VCAM-1) and thus reduce the ability of lymphocytes to adhere to the tumor vascular endothelial cells and migrate into the tumor tissues. TGF-β can suppress the activation and proliferation of tumor-infiltrating lymphocytes.[45]

Engagement of the PD-1 receptor on the immune cells by PD-L1 expressed by tumor cells may lead to a decrease in T cell activation, inhibition of T cell proliferation, and suppression of antitumor CD8 + T cell responses. In ovarian cancer, PD-L1 is detectable in about a third of advanced tumors, but most of the tumor-infiltrating lymphocytes express PD-1.[46,47] High-grade tumors have been reported to express PD-L1 to a greater extent than low-grade ovarian tumors (i.e. 42% *v* 8%). A higher expression of PD-L1 may be associated with a worse prognosis compared with patients with lower PD-L1 levels, although further investigations are warranted to define the prognostic value of PD-L1 expression in ovarian cancer.[46,47] Nonetheless, infiltrating CD3+, CD8+, and CD4 + T cells detected in the tumor tissues of approximately half of the ovarian cancers investigated ('hot tumors') were associated with better outcomes in patients with advanced ovarian cancer, with prolonged PFS and OS after treatment compared with patients with no infiltrates, suggesting that therapeutic approaches aimed at restoring active antitumor responses may provide benefit in this setting.[45–47] However, the complexity of the immune microenvironment associated with ovarian cancer, with the occurrence of immunosuppressive mediators and immunoregulatory cells (i.e. T regulatory cells [Treg] and myeloid-derived suppressor cells),[45–47,49] the potential for T cell exhaustion[49,50] and the effects of chemotherapy or surgery on antitumor immune responses, are all factors that need to be considered in the selection/sequencing of novel immunotherapeutic approaches and the design of combination regimens. Assessment of the pharmacodynamic effects of novel immunomodulatory approaches, currently ongoing in clinical trials, may also contribute to a better understanding of their impact on antitumor immune responses in patients with advanced ovarian cancer.

At initial clinical evaluation of PD-1/PD-L1 immune checkpoint inhibition therapies, both anti-PD-1 (i.e. nivolumab, pembrolizumab, PF-06801591) and anti-PD-L1 antibodies (i.e. atezolizumab, avelumab), have shown some single-agent, immunomodulatory and anti-tumor activity in patients with advanced ovarian cancer (7%-22%), albeit to a lower extent compared with other anti-PD-1/PD-L1 responsive tumor types (i.e. melanoma, non-small-cell lung cancer) (Table 3).[51–59] For immune checkpoint inhibition to work in any cancer, T cells must be present in the tumor microenvironment. A substantial proportion of patients with ovarian cancer are resistant to treatment with anti-PD-1/PD-L1 antibodies due to limited infiltration by antitumor immune cells, the activity of immunosuppressive cells and cytokines in the tumor microenvironment, and/or a low expression of PD-1/PD-L1, suggesting that multi-targeted combination approaches including PARP inhibitors, chemotherapeutic agents, angiogenesis inhibitors, radiation, other immunomodulatory agents, vaccines, dendritic cell therapy, adoptive T cell therapy, or other targeted therapy may be more effective to achieve disease control.[51–60]

Table 3. Single-agent treatment with PD-1/PD-L1 immune checkpoint inhibitors in patients with advanced ovarian cancer.

Agent	Study Phase	Patient Population	N	Outcomes	Reference
Anti-PD-1 antibodies					
Nivolumab	II	Platinum-resistant OvCa	20	ORR, 15%; durable CR in 2 patients; DCR, 45%; mPFS, 3.5 months; mOS, 20 months	Hamanishi et al., 2015
Nivolumab vs gemcitabine or pegylated liposomal doxorubicin	III (NINJA) randomized	Advanced or recurrent platinum-resistant OvCa	316	ORR, 8% *v* 13%; Duration of reponse: 18.7 *v* 7.4 months; mPFS, 2.1 *v* 3.8 months (HR, 1.46; $p = .002$); mOS: 10.1 *v* 12.1 months (HR, 1.03; $p = .808$).	Omatsu et al., 2020
Pembrolizumab	Ib	Advanced OvCa (73.1% of patients with ≥3 prior lines of therapy.	26, PD-L1+	ORR, 11.5%; mPFS, 1.9 months; mOS, 13.8 months	Varga et al., 2019
Pembrolizumab	II	Recurrent OvCa (1–3 prior lines of therapy, PFI/TFI 3–12 months)	285 (cohort A)	ORR, 7.4%; mDOR 8.2 months; DCR, 37.2%; mPFS, 2.1 months; mOS not reached	Matulonis et al., 2019
Pembrolizumab	II	Recurrent OvCa (4–6 prior lines of therapy, PFI/TFI ≥ 3 months)	91 (cohort B)	ORR, 9.9%; mDOR not reached; DCR, 37.4%; mPFS, 2.1 months; mOS 17.6 months	Matulonis et al., 2019
PF-06801591	I	Advanced OvCa	15	ORR, 20%; mPFS, 5.3 months; mOS, not reached	Johnson et al., 2019
Anti-PD-L1 antibodies					
Atezolizumab	Ia	Recurrent OvCa	12	ORR, 22%; durable PR in 2 patients; mPFS, 2.9 months; mOS, 11.3 months	Infante et al., 2016; Liu et al., 2019
Avelumab	Ib	Recurrent or refractory OvCa (median 3 prior lines of therapy)	125	ORR, 9.6%; mDOR, 10.4 months; DCR, 42%; mPFS, 2.6 months; mOS, 11.2 months	Disis et al., 2019

CR: complete response, DCR: disease control rate, mDOR: median duration of response, mOS: median overall survival, mPFS: median progression-free survival, OvCa: ovarian cancer, PD-1: programmed death receptor 1, PD-L1: PD ligand 1, PFI: platinum-free interval, PR: partial response, TFI: treatment-free interval.

Inhibition of DNA damage repair by a PARP inhibitor may induce an increase in the overall tumor mutational burden (TMB) and release of immunogenic, tumor-associated neoantigens. In addition, it promotes type-I interferon signaling, which in turn induces recruitment of T cells. The cell death induced by exposure to chemotherapeutic agents also generates new, tumor-related, immunogenic determinants that can facilitate the antitumor immune responses restored by PD-1/PD-L1 inhibition.[60]

VEGFR inhibition may result in tumor vessel normalization and facilitate migration of immune cells into the tumor microenvironment.[11,45] Consistently, VEGF inhibition by bevacizumab in combination with atezolizumab was shown to attenuate progression of platinum-resistant ovarian cancer through synergic anti-tumor activity, based on *in vitro* and *in vivo* analyses.[61] Clinical activity has also been observed with nivolumab plus bevacizumab combination treatment in a phase II trial conducted in patients with recurrent ovarian cancer.[62] Furthermore, preclinical investigations have shown that treatment with niraparib increased the activity of IFN-γ and IFN-γ signaling pathways as well as intra-tumor infiltration by CD8+ and CD4 + T cells. Combined administration of niraparib and an anti-PD-1 antibody in breast and ovarian cancer mouse models demonstrated synergic antitumor activity against both mutated *BRCA*+ and wild-type *BRCA* tumors, indicating a potential applicability of this combination.[63] In addition, a study demonstrated that PARP inhibition by olaparib or talazoparib can induce upregulation of PD-L1 expression in breast cancer cell lines *in vitro* and in xenograft tumor models *in vivo*.[64] Block of PD-L1 by a targeted antibody was found to restore sensitivity of PARP inhibitor-treated cancer cells to T-cell-mediated cytotoxicity. Combined administration of a PARP inhibitor and an anti-PD-L1 antibody produced greater antitumor activity *in vivo* versus either agent alone in this animal model, suggesting potential benefit from combined treatment with these agents in humans.[64]

In addition to PD-1/PD-L1 immune checkpoint inhibitors, other immunotherapeutic approaches such as dendritic cell vaccines, tumor-infiltrating lymphocytes (TILs), and chimeric antigen receptor (CAR)-T cells are being pursued for the treatment of advanced ovarian cancer.[60,65–69] Investigational, autologous ovarian cancer vaccines generated by pulsing dendritic cells with oxidized, whole-tumor-cell lysates obtained from individual patients have been evaluated in a pilot study, following intranodal injection in immune-naïve patients with recurrent, platinum-pretreated advanced ovarian cancer.[65] A subgroup of patients also received IV bevacizumab to enhance tumor infiltration by immune cells and low-dose cyclophosphamide to decrease infiltration by Treg cells. Vaccination was associated with a tolerable safety profile, high-affinity T-cell responses to autologous tumor antigens, and prolonged survival. Anti-tumor antigen responses were higher in vaccinated patients who had received concomitant treatment with cyclophosphamide. The OS at 2 years was greater in vaccinated patients (78%) who had received bevacizumab plus cyclophosphamide compared with an historical, institutional group of matched patients treated only with bevacizumab plus cyclophosphamide (44%). Although different factors (i.e. tumor sample availability, low lysate immunogenicity, complex production process) may limit the clinical applicability of autologous,

dendritic cell vaccines for each patient, these findings indicate the feasibility of inducing beneficial, tumor-specific immune responses in advanced ovarian cancer.[65]

In a pilot study, adoptive cell therapy with TILs and progressively decreasing IV doses of IL-2 in patients with metastatic, platinum-resistant ovarian cancer, was associated with a manageable toxicity and early signals of clinical activity, although all treated patients ultimately progressed, mostly due to the development of new lesions. Infused TILs were found to express biomarkers potentially associated with T-cell exhaustion (i.e. LAG3 and PD-1), while tumor tissues demonstrated expression of major histocompatibility complex class II antigens and PD-L1, suggesting activation of inhibitory immune checkpoint pathways.[66]

Results from an adoptive immunotherapy study of gene-modified CAR T cells redirected to the tumor-associated antigen folate receptor alpha (FRα) plus high-dose IL-2 showed large numbers of transferred T cells in the peripheral blood of treated patients within the first 2 days after infusion, followed, however, by a decline to very low levels within 1 month and mostly no localization in tumors.[67] A lack of responsiveness to growth factors *in vivo*, T-cell exhaustion after prolonged *in vitro* culture, and/or the IV route of administration with intra-organ sequestration may have contributed to the limited *in vivo* survival and tumor homing of the transferred, gene-modified T cells observed in this study. Optimization of *in vitro* culture conditions and costimulatory signals as well as selection of an IP delivery route may contribute to improved survival and *in vivo* antitumor activity of CAR T cells against ovarian cancers.[67] In other studies, CAR T cells targeted to the tumor-associated antigens mesothelin or mucin 16 (MUC16), known to be overexpressed on ovarian cancer cells, demonstrated cytotoxic activity *in vitro* and antitumor activity *in vivo*, resulting in growth inhibition of ovarian tumors in preclinical animal models.[68,69] Combinations with immunomodulatory signals, such as costimulation through CD28 or PD-1/PD-L1 immune checkpoint inhibition, or with growth factors (i.e. IL-12), can contribute to enhance the *in vivo* efficacy of CAR T-cell-based approaches.[68,69]

Combination studies of chemotherapy, PARP inhibitors, anti-PD-1/PD-L1 antibodies, and/or VEGFR inhibitors in patients with advanced ovarian cancer

Based on the findings outlined above, multiple combination strategies including PARP inhibition and/or an anti-PD-1/PD-L1 antibody and/or a VEGFR inhibitor are being evaluated in patients with a) newly diagnosed, b) relapsed, platinum-sensitive or c) platinum-resistant disease (Table 4).

Chemotherapy-based combination regimens (± PARP inhibitor ± anti-PD-1/PD-L1 antibody ± VEGFR inhibitor)

PD-1/PD-L1 targeted immune checkpoint inhibitors are being administered in combination with standard of care platinum/taxane-based chemotherapy in various phase III trials for the treatment of patients with stage III–IV, newly diagnosed ovarian cancer with or without bevacizumab, followed by maintenance therapy with a PARP inhibitor with or without an anti-PD-1/PD-L1 antibody and/or bevacizumab. Details of these trials are presented in Table 4.

JAVELIN ovarian PARP 100, which was a phase III study in newly diagnosed ovarian cancer patients, evaluating avelumab in combination with platinum-based chemotherapy followed by maintenance with avelumab and talazoparib versus chemotherapy plus talazoparib maintenance or chemotherapy plus bevacizumab followed by bevacizumab maintenance, was terminated early as the extent of benefit observed with avelumab did not support continuation of this study in an unselected patient population.

Results from the randomized, phase III trial IMagyn050/GOG 3015/ENGOT-ov39 conducted in newly diagnosed patients with stage III–IV ovarian cancer have shown that addition of a PD-L1 inhibitor, atezolizumab, to standard chemotherapy (carboplatin/paclitaxel) plus bevacizumab followed by maintenance with bevacizumab did not significantly improve mPFS (primary endpoint) in the intent-to-treat population (19.5 *v* 18.4 months; hazard ratio, 0.92) or in PD-L1-positive patients with ≥1% expression (20.8 *v* 18.5 months; hazard ratio, 0.80). However, an exploratory analysis suggested a trend toward improved mPFS with addition of atezolizumab in the subgroup of patients with PD-L1 expression ≥5%.[70]

Table 4 summarizes phase III trials being conducted in patients with recurrent, platinum-sensitive disease, which are evaluating chemotherapy in combination with a PD-1/PD-L1 inhibitor with or without bevacizumab and maintenance treatment with an anti-PD-1/PD-L1 antibody plus/minus a PARP inhibitor and/or bevacizumab.

PARP inhibitor + VEGFR inhibitor combinations

VEGFR inhibition can produce impairment of homologous recombination DNA repair with downregulation of *BRCA1/2* and *RAD51* in addition to inhibition of tumor-associated angiogenesis, potentially sensitizing target cells to the antitumor activity of PARP inhibitors.[71] Results from randomized trials have demonstrated this combination as superior to PARP inhibition alone.[72,73]

Cediranib is a small-molecule, VEGFR 1–3 tyrosine kinase inhibitor, reported to induce sensitivity to PARP inhibitors (i.e. olaparib) by inducing tumor hypoxia and inhibiting PDGFR, which result in decreased expression of BRCA1/2 and RAD51 and reduced activity of HR DNA repair in target cells.[71] In a randomized phase II study, combination treatment with cediranib and olaparib demonstrated a significant improvement in mPFS and overall survival versus olaparib alone in patients with germline *BRCA* wild-type/unknown, relapsed, platinum-sensitive ovarian cancer.[72] A significant improvement in mPFS with VEGF plus PARP inhibition has also been reported with bevacizumab plus niraparib in patients with recurrent, platinum-sensitive disease, in the randomized phase II trial NSGO-AVANOVA2/ENGOT-ov24.[73]

Thus, phase III trials have been initiated to evaluate combinations of VEGFR and PARP inhibition for potential additive/synergistic effects in relapsed platinum-sensitive or platinum-resistant/refractory, advanced ovarian cancer (Table 4). Combination of cediranib with olaparib in the randomized, phase III NRG-GY004 trial has recently demonstrated an mPFS (primary endpoint) comparable rather than significantly improved versus standard platinum-based chemotherapy with

Table 4. Investigational combination regimens in patients with advanced ovarian cancer.

Clinical Trial	CT	P	I	A	Treatment	Patient Population[a]	Phase	Primary EP
Chemotherapy-based combinations (CT ± PARPi ± anti-PD-1/PD-L1 antibody ± VEGFRi)								
FIRST/ENGOT-ov44 (NCT03602859)		m			Platinum-based CT + TSR-042 (dostarlimab) followed by niraparib + TSR-042 vs CT followed by niraparib maintenance vs CT	1st line, stage III–IV OvCa	Randomized, double-blind, phase III	PFS
KEYLYNK-001/ENGOT-ov43 (NCT03740165)		m			CT (carboplatin/paclitaxel) + pembrolizumab followed by olaparib maintenance or CT (carboplatin/paclitaxel) + pembrolizumab vs CT (carboplatin/paclitaxel) (study arms may include bev)	1st line, *BRCA* non-mutated OvCa	Randomized, double-blind, phase III	PFS, OS
IMagyn050/GOG 3015/ENGOT-ov39 (NCT03038100)					CT (carboplatin/paclitaxel) + atezolizumab + bev followed by maintenance atezolizumab + bev vs CT (carboplatin/paclitaxel) + bev followed by bev	Stage III–IV OvCa after tumor-reductive surgery	Randomized, double-blind, phase III	PFS, OS
DUO-O/ENGOT-ov46 (NCT03737643)		m		m	CT + durvalumab followed by maintenance durvalumab + olaparib + optional bev	Newly diagnosed OvCa, *BRCA*-mutated	Randomized, open-label, phase III	PFS
DUO-O/ENGOT-ov46 (NCT03737643)		m			CT + durvalumab + bev followed by maintenance durvalumab + olaparib + bev vs CT + durvalumab + bev followed by maintenance durvalumab + bev vs CT + bev followed by maintenance bev	Newly diagnosed OvCa, non *BRCA*-mutated	Randomized, double-blind, phase III	PFS
ATHENA/ENGOT-ov45 (NCT03522246)		m		m	Platinum-based CT followed by maintenance rucaparib + nivolumab vs rucaparib vs nivolumab vs placebo	Responders to front-line chemotherapy	Randomized, double-blind, phase III	PFS
ICON 9 (NCT03278717)		m		m	Platinum-based CT followed by maintenance olaparib + cediranib vs platinum-based CT followed by maintenance olaparib	Relapsed, platinum-sensitive OvCa (responders ≥4 cycles of CT)	Randomized, open-label, phase III	PFS, OS
ANITA/ENGOT-ov41/GEICO 69-O (NCT03598270)		m			Platinum-based CT (investigator's choice) + atezolizumab followed by maintenance niraparib + atezolizumab vs CT (investigator's choice) followed by maintenance niraparib	Recurrent OvCa, TFIp >6 mos	Randomized, double-blind, phase III	PFS
ATALANTE (NCT02891824)					Platinum-based CT + atezolizumab + bev ± maintenance atezolizumab + bev vs platinum-based CT + bev followed by maintenance bev	Recurrent OvCa, TFIp >6 mos	Randomized, double-blind, phase III	PFS
NRG-GY009 (NCT02839707)					Pegylated liposomal doxorubicin (PLD) + atezolizumab or PLD + atezolizumab + bevacizumab vs PLD + bevacizumab	Platinum-resistant OvCa	Randomized, open-label, phase II–III	PFS, OS
PARPi + VEGFRi combinations								
NSGO-AVANOVA2/ENGOT-ov24 (NCT02354131)					Niraparib + bev vs niraparib	Relapsed, platinum-sensitive OvCa	Randomized, open-label, phase II	PFS
NRG-GY004 (NCT02446600)					Olaparib + cediranib or olaparib vs standard platinum-based CT	Relapsed, platinum-sensitive OvCa	Randomized, open-label, phase III	PFS
NRG-GY005/COCOS (NCT02502266)					Cediranib + olaparib vs cediranib vs SOC CT (physician's choice)	Recurrent, platinum-resistant/refractory OvCA (high-grade for *BRCA1/2* non-mutation carriers)	Randomized, open-label, phase III	PFS, OS
OCTOVA (NCT03117933)					Olaparib + cediranib vs olaparib vs paclitaxel	Platinum-resistant OvCa	Randomized, open-label, phase II	PFS
PARPi + anti-PD-1/PD-L1 antibody combinations								
TOPACIO/KEYNOTE-162 (NCT02657889)					Niraparib + pembrolizumab	Recurrent OvCa	Open-label, phase I–II	ORR

(*Continued*)

Table 4. (Continued).

Clinical Trial	CT	P	I	A	Treatment	Patient Population[a]	Phase	Primary EP
Javelin PARP Medley (NCT03330405)					Talazoparib + avelumab	Recurrent, platinum-sensitive including *BRCA*-mutated OvCa	Open-label, phase Ib-II	ORR
NCT02660034					BGB-290 (pamiparib) + BGB-A317 (tislelizumab)	Recurrent, platinum-sensitive (TFIp >6) mos), high-grade OvCa	Open-label, phase I	ORR
ARIES (NCT03824704)					Rucaparib + nivolumab	Relapsed, platinum-sensitive OvCa	Open-label, phase II	ORR
NCT02484404					Olaparib + durvalumab	Recurrent, platinum-resistant OvCa	Open-label, phase II	ORR
PARPi + anti-PD-1/PD-L1 antibody + VEGFRi combinations								
NCT02484404					Durvalumab + olaparib + cediranib, durvalumab + olaparib, and durvalumab + cediranib	Recurrent, platinum-sensitive or resistant OvCa	Non-randomized, open-label, phase II	ORR
MEDIOLA (NCT02734004)					Durvalumab + olaparib + bevacizumab and durvalumab + olaparib	Relapsed, platinum-sensitive OvCa	Non-randomized, open-label, phase II	ORR
NCT02873962					Nivolumab + rucaparib + bevacizumab, nivolumab + bevacizumab	Relapsed, platinum-sensitive or resistant OvCa	Non-randomized, open-label, phase II	ORR
NSGO/AVANOVA-Triplet (NCT03806049)					TSR-042 + niraparib + bevacizumab, niraparib + bevacizumab, and carboplatin + paclitaxel	Recurrent, platinum-sensitive OvCa	Randomized, open-label, phase III	PFS
OPAL (NCT03574779)					TSR-042 + niraparib + bevacizumab	Recurrent, platinum-resistant OvCa	Open-label, phase II	ORR
anti-PD-1/PD-L1 antibody + VEGFRi combination								
NCT04068974					Camrelizumab + apatinib	Recurrent, platinum-resistant OvCa	Open-label, phase II	ORR

[a]Clinical trials may include patients with other tumor types in addition to patients with advanced ovarian cancer. A: angiogenesis inhibition, bev: bevacizumab, CT: chemotherapy, m: maintenance, EP: endpoint, I: PD-1/PD-L1 immune checkpoint inhibition, ORR: objective response rate, OS: overall survival, OvCa: ovarian cancer, P: PARP inhibition, PARPi: PARP inhibitor, PD-1: programmed death 1 receptor, PD-L1: PD-ligand 1, PFS: progression-free survival, SOC: standard of care, TFIp: platinum treatment-free interval, VEGFRi: vascular endothelial growth factor receptor inhibitor.

carboplatin/paclitaxel, carboplatin/gemcitabine, or carboplatin/pegylated liposomal doxorubicin (10.4 *v* 10.3 months, hazard ratio 0.86), in the intent-to-treat population of patients with relapsed, platinum-sensitive OvCa.[74] However, in a planned subset analysis of patients with germline *BRCA* mutations, the hazard ratio for improvement in mPFS versus chemotherapy was 0.55 for cediranib plus olaparib and 0.63 for olaparib alone.[74] Further phase II or III clinical trials are in progress evaluating cediranib in various combinations with PARP inhibitors, chemotherapy, or anti-PD-1/PD-L1 antibodies.

PARP inhibitor + anti-PD-1/PD-L1 antibody ± VEGFR inhibitor combinations

As previously discussed, preclinical studies have demonstrated synergy between PARP inhibitors and immune checkpoint inhibitors in mediating antitumor activity.[63,64] Thus, a number of clinical trials are currently evaluating combination treatment with these two classes of agents in patients with recurrent ovarian cancer, including niraparib plus pembrolizumab, talazoparib plus avelumab, BGB-290 (pamiparib) plus BGB-A317 (tislelizumab), rucaparib plus nivolumab, and olaparib plus durvalumab. In addition, multiple phase II or III studies are assessing triple combinations of a PARP inhibitor with an anti-PD-1/PD-L1 antibody and a VEGFR inhibitor in platinum-sensitive or resistant disease (Table 4).

Results from the phase I–II study (TOPACIO/Keynote-162) of niraparib in combination with pembrolizumab showed an ORR of 18% in patients with recurrent, advanced ovarian cancer, with no new safety signals from the combination treatment. The majority of patients had platinum-resistant/refractory disease.[75] This compares with historical ORRs of ≤10% with PD-1 checkpoint inhibitor treatment (irrespective of PD-1 levels) or PARPi monotherapy in similar patient populations without *BRCA*-mutations.[75]

Initial findings from the phase II study (NCT02484404) of olaparib and durvalumab in patients with mostly platinum-resistant, recurrent disease, showed an overall ORR of ~15%, with responses in both *BRCA*-mutated and *BRCA*-wild type patients. Grade 3–4 anemia and lymphopenia were reported in 26% and 14% of patients, respectively. Dose reductions of olaparib were required in <1% of patients.[76] Preliminary results from the same phase II study of a triple combination of olaparib, durvalumab, and cediranib in a small number of patients with recurrent ovarian cancer have shown tolerability, antitumor activity with partial responses, and correlation of clinical benefit with PD-L1 expression levels in tumors.[77] Furthermore, a triple combination of olaparib, durvalumab, and bevacizumab investigated in the phase II, non-randomized MEDIOLA trial, in patients with relapsed, platinum-sensitive ovarian cancer (non-germline *BRCA*-mutated) demonstrated a high 24-week disease control rate (77.4%) and confirmed ORR (77.4%), with a mPFS of 14.7 months. In the olaparib plus durvalumab arm, the ORR was 31.3% and the mPFS was 5.5 months.[78,79] Anemia, hypertension, fatigue, increased lipase levels, and neutropenia were the grade ≥3 AEs most frequently observed with the triple combination; 16% of patients discontinued one or more study drugs in this combination regimen.[79]

III. Targeting tumor-associated antigens and signaling pathways in ovarian cancer

A number of novel agents to tumor targets associated with ovarian cancer growth and progression are currently in clinical development, to identify new options for single-agent or combination treatment in patients with advanced ovarian cancer (Table 5). Details of the clinical studies in progress with these agents are presented in Table 6.

Folate receptor alpha (FRα)

FRα is a transmembrane glycoprotein mediating transport of folate into cells, which is overexpressed in the majority of

Table 5. Targeted agents in development for the treatment of patients with advanced ovarian cancer.

Agent	Target/MOA	Structure	Company	Phase
Folate receptor α (FRα) targeting				
Mirvetuximab soravtansine (IMGN853) (M9346A antibody + maytansinoid DM4)	FRα/microtubule inhibitor	ADC	ImmunoGen	I–III
MORAb-202 (farletuzumab + eribulin)	FRα/microtubule inhibitor	ADC	Eisai	I–II
Tissue factor targeting				
Tisotumab vedotin (HuMax-TF-ADC) (antibody + MMAE)	Tissue factor targeting/microtubule inhibitor	ADC	Genmab/Seattle Genetics	II
PTK7 targeting				
PF-06647020 (antibody + auristatin 0101)	PTK7 targeting/microtubule inhibitor	ADC	Pfizer/AbbVie	I
Protein kinase inhibition				
Adavosertib (AZD1775)	WEE1 TK inhibitor	SMI	AstraZeneca	II
Alpelisib (BYL719)	PI3K-α inhibitor	SMI	Novartis	Ib
Ralimetinib (LY2228820 dimesylate)	p38 MAPK1 inhibitor	SMI	Lilly	Ib/II
Prexasertib (LY2606368)	CHK 1/2 inhibitor	SMI	Lilly	II
AZD6738	ATR PK inhibitor	SMI	AstraZeneca	II
Berzosertib (M6620, VX-970/VE-822)	ATR PK inhibitor	SMI	Merck Serono	II

ADC: antibody-drug conjugate, ATR: ataxia telangiectasia mutated and Rad3-related kinase, CHK: cell cycle checkpoint, FGF: fibroblast growth factor, HDAC: histone deacetylase, Hsp: heat shock protein, MAPK: mitogen-activated protein kinase, MMAE: monomethyl auristatin E, MOA: mechanism of action, PDGF: platelet-derived growth factor, PI3K: phosphatidylinositol 3-kinase, PK: protein kinase, SMI: small-molecule inhibitor, TK: tyrosine kinase, VEGF: vascular endothelial growth factor, VEGFR2: VEGF receptor 2.

Table 6. Clinical trials evaluating emerging agents for the treatment of patients with advanced ovarian cancer.

Clinical Trial	Treatment	Patient Population[a]	Phase	Primary EP
Targeting folate receptor α (FRα)				
FORWARD I (NCT02631876)	Mirvetuximab soravtansine vs CT of choice (paclitaxel, pegylated liposomal doxorubicin or topotecan)	Platinum-resistant, FRα-positive OvCa	Randomized, open-label phase III	PFS
MIRASOL (NCT04209855)	Mirvetuximab soravtansine vs CT of choice (paclitaxel, pegylated liposomal doxorubicin, or topotecan)	Platinum-resistant OvCa with high FRα expression	Randomized, open-label phase III	PFS
SORAYA (NCT04296890)	Mirvetuximab soravtansine	Platinum-resistant OvCa with high FRα expression	Single-arm, open-label phase III	ORR
KEYNOTE PN409/FORWARD II (NCT02606305)	Mirvetuximab soravtansine + carboplatin or bev or pegylated liposomal doxorubicin or pembrolizumab or carboplatin/bev	FRα-positive OvCa	Phase Ib-II	ORR
NCT03552471	Mirvetuximab soravtansine + rucaparib	FRα-positive, recurrent *BRCA*-mutated or platinum-resistant OvCa	Phase I	RP2D
NCT04300556	Morab-202	FRα-positive, platinum-resistant OvCa and other solid tumors	Phase I–II	Safety, RP2D, ORR
Tissue factor (TF) targeting				
NCT02552121	Tisotumab vedotin	Relapsed/metastatic tumors known to express TF	Phase I–II	Safety, RP2D
InnovaTV 208 (NCT03657043)	Tisotumab vedotin (standard or dose-dense regimen)	Platinum-resistant OvCa	Randomized, open-label phase II	ORR
Protein kinase inhibition				
NCT03579316	Adavosertib single agent or + olaparib	Recurrent OvCa with progression after prior PARPi therapy	Randomized, open-label phase II	ORR
NCI MATCH screening trial/ subprotocol Z1I BRCA-mutated tumors (NCT02465060)	Single-agent adavosertib	Advanced, *BRCA*-mutated, refractory OvCa	Phase II	ORR
NCT01623349	Alpelisib (BYL 719) or buparlisib (BKM120) + olaparib	Recurrent high-grade OvCa after prior platinum-based therapy	Phase Ib	MTD, RP2D
NCT01663857	Ralimetinib + CT (gemcitabine and carboplatin) vs CT	Recurrent OvCa, TFIp >6 months	Randomized, double-blind, phase Ib-II	PFS
NCT02203513	Prexasertib (LY2606368)	Recurrent *BRCA*-mutated and *BRCA*-non mutated OvCa	Phase II	ORR
NCT03414047	Prexasertib (LY2606368)	Recurrent, *BRCA*-mutated and *BRCA*-non mutated, platinum resistant/ refractory OvCa	Phase II	ORR
CAPRI (NCT03462342)	AZD6738 + olaparib	Recurrent platinum-sensitive and platinum-resistant OvCa	Phase II	Safety
NCT02595892	Berzosertib (M6620) + gemcitabine vs gemcitabine	Recurrent, platinum-resistant OvCa	Randomized, open-label phase II	PFS
NCT02627443	Berzosertib (M6620) + carboplatin and gemcitabine	Recurrent, platinum-sensitive OvCa	Phase I	MTD, safety

[a]Clinical trials may include patients with other tumor types in addition to advanced ovarian cancer. AE: adverse event, Bev: bevacizumab, CT: chemotherapy, DLT: dose-limiting toxicity, EP: endpoint, MTD: maximum tolerated dose, ORR: objective response rate, OvCa: ovarian cancer, PARPi: PARP inhibitor, PFS: progression-free survival, q2 weeks: every 2 weeks, q3 weeks: every 3 weeks, RP2D: recommended phase II dose, SOC: standard of care, TFIp: platinum treatment-free interval.

epithelial ovarian cancers but absent in normal epithelial cells of the ovary.[80] Such selective expression in tumor cells and the ability to internalize following ligand binding make FRα a suitable target for antibody-drug conjugates (ADCs) designed to deliver cytotoxic payloads to tumor cells.[80]

Mirvetuximab soravtansine is an FRα-targeted ADC composed of the anti-FRα M9346A antibody and the microtubule-disrupting agent maytansinoid DM4. The presence of a cleavable linker also allows release of active DM4 molecules and killing of proximal tumor cells.[80,81] Combination treatment with mirvetuximab soravtansine plus carboplatin followed by maintenance with mirvetuximab soravtansine had an acceptable tolerability profile in a phase I study of patients with recurrent, platinum-sensitive ovarian cancer, with an ORR of 71% and median PFS of 15 months. The most frequent AEs were nausea, diarrhea, thrombocytopenia, blurred vision, and fatigue (mostly ≤ grade 2).[80]

The randomized phase III FORWARD I trial evaluated safety and efficacy of mirvetuximab soravtansine versus chemotherapy of choice in patients with FRα-positive, platinum-resistant ovarian cancer, who had received up to three lines of prior treatment.[81] Although the response rate was higher in the experimental arm, the study did not meet the primary endpoint of a significant improvement in mPFS. Nonetheless, patients with high levels of FRα expression treated with mirvetuximab soravtansine had longer mPFS (4.8 *v* 3.3 months) and a higher ORR (24% *v* 10%), with less grade ≥3 AEs and treatment discontinuations due to AEs compared with chemotherapy, thus suggesting a potentially favorable risk/benefit profile in this patient population.[82] The most frequent AEs reported with

mirvetuximab soravtansine in this study were nausea (54%), diarrhea (44%), and blurred vision (43%).[82] Two phase III trials, MIRASOL and SORAYA, are further evaluating mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer and high FRα expression. In MIRASOL, safety and efficacy of mirvetuximab soravtansine are assessed versus chemotherapy of choice with paclitaxel, pegylated liposomal doxorubicin, or topotecan (primary endpoint, mPFS) (Table 6).

Furthermore, mirvetuximab soravtansine is being evaluated in combination with chemotherapy, bevacizumab, the anti-PD-1 antibody pembrolizumab, or the PARP inhibitor rucaparib in phase I–II studies, to identify potential synergies with these inhibitors (Tab
le 6). Results from cohorts of patients with platinum-resistant, ovarian cancer treated with mirvetuximab soravtansine and bevacizumab in the FORWARD II study have shown an ORR of 39% in all patients (mPFS, 6.9 months) and 56% in bevacizumab-naïve patients with medium/high FRα expression (≥50% positive cells) (mPFS, 9.9 months). AEs were generally mild or moderate in severity; 9% of patients developed grade 1–2 pneumonitis.[83]

In addition, a triple combination of mirvetuximab soravtansine with carboplatin and bevacizumab (followed by mirvetuximab soravtansine/bevacizumab maintenance), in a phase Ib/II study of patients with recurrent, platinum-sensitive ovarian cancer and medium/high FRα expression, was associated with a manageable safety profile, confirmed responses in 81% of patients (median duration, 10.7 months) and a mPFS of 12.0 months. The most frequently reported treatment-related AEs were diarrhea, nausea, fatigue, and blurred vision, consistent with the known safety profile of mirvetuximab soravtansine. Grade 2 peripheral neuropathy was observed in 22% of patients.[84]

The ADC MORAb-202 consists of the humanized anti-FRα antibody farletuzumab conjugated to the microtubule-targeted agent eribulin (maleimido-PEG2-valine-citrulline-*p*-aminobenzylcarbamyl-eribulin) through reduced inter-chain disulfide bon
ds. Preclinical studies demonstrated durable antitumor responses in human cell lines and patient-derived xenograft tumor models, supporting evaluation of this novel ADC for the treatment of patients with FRα-positive tumors.[85] Administration of MORAb-202 was associated with complete and partial responses in patients with advanced ovarian cancer enrolled in a first-in-human, phase I study. Leukopenia and neutropenia, observed in approximately half of the patients, were the most frequent treatment-related AEs.[86] Further evaluation of MORAb-202 is ongoing in patients with FRα-positive, platinum-resistant ovarian cancer and other selected tumor types in advanced stage (endometrial, non-small-cell lung, and triple-negative breast cancer) (Table 6).

Tissue factor (TF)

TF, usually involved as a cofactor in the coagulation process, can be abnormally expressed on the surface of cancer cells in various tumor types and thus provide a potential new target for anticancer therapy.[87,88] Tisotumab vedotin is a TF-targeted ADC consisting of a human IgG1 antibody conjugated to monomethyl auristatin E (MMAE) through a protease-cleavable valine citrulline linker.[87] Durable tumor responses were achieved with tisotumab vedotin in TF-positive xenograft solid tumor models, including patient-derived xenografts.[87]

Preliminary findings from a phase I–II study of tisotumab vedotin in patients with advanced solid malignancies, unselected for predefined TF expression levels, showed an ORR of ~16%. The most common AEs were epistaxis, fatigue, nausea, alopecia, and conjunctivitis; grade ≥3 AEs (fatigue, anemia, abdominal pain, and hypokalemia) were reported in ≤10% of patients.[87] A randomized, open-label phase II study (innovaTV 208) is evaluating a standard and a dose-dense regimen of tisotumab vedotin in patients with advanced, platinum-resistant ovarian cancer.[89]

Protein tyrosine kinase 7 (PTK7)

PTK7 is a catalytically inactive receptor tyrosine kinase, involved in the Wnt signaling pathway, which was shown to be enriched in tumor-initiating cells (TICs) in patient tumor xenografts.[90] Thus, PTK7 represents a tumor target that can lead to elimination of cancer cells responsible for tumor recurrence and dissemination. The anti-PTK7 ADC PF-06647020 consists of a humanized, monoclonal antibody joined to the auristatin microtubule inhibitor Aur0101 by a cleavable valine-citrulline-based linker. Following internalization and cleavage, auristatin-0101 inhibits tubulin polymerization leading to apoptotic cell death in target cells.[90] In preclinical, patient-derived tumor xenograft models, PF-06647020 induced durable responses and showed greater efficacy compared with chemotherapy.[90]

Results from a phase I study of PF-06647020 demonstrated a manageable safety profile, with a disease control rate of 73% (ORR, 27%) in patients with advanced ovarian cancer.[91] The majority of the treatment-related AEs were grade 1–2, including most frequently nausea, alopecia, fatigue, headache, neutropenia, and vomiting.[91] Biomarker analysis showed that clinical responses to PF-06647020 correlated with higher baseline PTK7 tumor expression levels.[92]

Protein kinase-mediated pathways

The WEE1 kinase is a key intracellular checkpoint at the G_2-M transition that mediates arrest of the cell cycle to allow for pre-mitotic DNA repair in the G_2 phase. Differently from normal cells, DNA repair in cancer cells occurs more frequently in G_2 than in G_1 arrest, thus conferring tumor selectivity to WEE1 targeting. Inhibition of WEE1 in the presence of DNA damaging agents can result in mitotic catastrophe due to initiation of mitosis with unrepaired lethal DNA damage.[93] Consistently, preclinical studies have demonstrated increased cell death, reduced tumor burden, and prolonged survival in experimental animal models following WEE1 inhibition.[93]

Adavosertib (AZD1775) is a WEE1 tyrosine kinase inhibitor which has demonstrated antitumor activity in a small number of treatment-refractory patients with *BRCA*-mutated tumors including ovarian cancer.[94] Supraventricular tachyarrhythmia and myelosuppression were reported as dose-limiting toxicities, while myelosuppression and diarrhea were common treatment-related AEs.[94] Evaluation of adavosertib plus carboplatin in patients with *TP53*-mutated, platinum-resistant/refractory ovarian cancer showed an ORR of 43% and a median PFS of 5.3 months, with responses lasting more than 31 months in 2 of

24 patients. The most frequent, grade 3–4, treatment-related AEs were thrombocytopenia and neutropenia.[95] Further trials are in progress investigating combination treatment with adavosertib and olaparib in a phase II study of patients with ovarian cancer progressing after prior PARP inhibitor therapy, and adavosertib monotherapy in the phase II NCI MATCH screening trial/subprotocol Z1I in patients with *BRCA*-mutated tumors.[96]

Alpelisib (BYL719) is a small-molecule, selective inhibitor of the phosphatidylinositol 3-kinase (PI3K) α subunit, approved by the FDA for the treatment of hormone receptor positive, HER2-negative, PIK3CA mutation-positive breast cancer.[97] Preclinical studies have shown that PI3K inhibitors may impair homologous recombination repair and sensitize ovarian cancer cells to PARP inhibitors.[98] Results from a phase Ib combination study of alpelisib with olaparib, in patients with recurrent ovarian cancer after prior platinum-based therapy, indicated a partial response rate of 36% and stable disease in 50% of patients. Treatment-related grade 3–4 AEs included hyperglycemia, nausea, and increased alanine aminotransferase levels. Hyperglycemia and neutropenic fever occurred as dose-limiting toxicities.[98]

Ralimetinib mesylate (LY2228820 dimesylate) is a small-molecule inhibitor of p38α and β mitogen-activated protein kinase 1 (MAPK1), a kinase that may facilitate cell survival and resistance to standard treatment by modulation of cytokine production in the tumor microenvironment. Pharmacodynamic studies showed inhibition of p38 MAPK-induced phosphorylation of MAP kinase-activated protein kinase 2 (MAPKAP-K2) by ralimetinib in patient peripheral blood mononuclear cells.[99] Preliminary evaluation of ralimetinib in a randomized phase Ib-II study in combination with gemcitabine and carboplatin chemotherapy demonstrated a significant, although limited prolongation in median PFS (10.3 *v* 7.9 months), but no significant difference in ORR and median OS, in patients with recurrent, platinum-sensitive ovarian cancer. Neutropenia, thrombocytopenia, and anemia were the most frequent grade 3–4 AEs in both treatment arms; grade 3–4 elevations in alanine aminotransferase levels were observed more frequently in patients receiving the triple combination.[100]

A further, novel kinase inhibitor that has shown activity against ovarian cancer in preclinical and early clinical studies is prexasertib (LY2606368), a selective, ATP-competitive inhibitor of the cell cycle checkpoint kinase 1 and 2 (CHK 1/2), which are expressed at higher levels in cancer cells compared with normal tissues.[101,102] Inhibition of CHK 1/2 activity leads to replication catastrophe, thereby inducing cell death and sensitizing cancer cells to the antitumor activity of PARP inhibitors. Prexasertib in combination with olaparib has shown antitumor activity in patient-derived, ovarian cancer xenograft models with acquired resistance to olaparib and in olaparib-sensitive models with an increase in the extent and durability of the antitumor responses observed.[101] Initial findings from a phase II study of prexasertib in patients with recurrent, mostly platinum-resistant/refractory, *BRCA*-non mutated, high-grade ovarian cancer demonstrated a 33% response rate in evaluable patients.[102] Neutropenia, leukopenia, and thrombocytopenia were the most frequent grade 3–4 AEs associated with treatment (≥25% of patients). However, grade 4 neutropenia observed in ~79% of cases after first dose administration appeared transient and improved without growth factor therapy.[102] Further evaluation of prexasertib is in progress in patients with advanced, *BRCA*-mutated ovarian cancer.[103]

Acting in concert with CHKs (i.e. CHK1), the ataxia telangiectasia mutated and Rad3-related (ATR) serine threonine protein kinase contributes to genomic stability by regulating initiation of DNA replication and DNA repair.[104] The ATR kinase inhibitor AZD6738 is an ATP-competitive, small-molecule inhibitor of ATR which inhibits phosphorylation of CHK1 Ser345, leading to an impairment in cell cycle progression and cell proliferation.[105] Synergistic activity was observed against tumor cells with AZD6738 and DNA-damaging agents (i.e. cisplatin, carboplatin, gemcitabine), ionizing radiation, or PARP inhibitors.[106] A phase II study is assessing AZD6738 in combination with olaparib in patients with recurrent platinum-sensitive or platinum-resistant ovarian cancer.

Consistent with its mechanism of action, the selective ATR kinase inhibitor berzosertib (M6620/VX-970/VE-822) has shown enhanced induction of double-strand DNA breaks and antitumor activity in combination with the topoisomerase I inhibitor topotecan in patients with platinum-refractory, solid tumors.[107,108] The most frequent treatment-related AEs were hematologic, with grade 3–4 anemia, leukopenia, and neutropenia observed in 19% and thrombocytopenia in 10% of treated patients.[108] Preliminary results from a randomized phase II study in platinum-resistant ovarian cancer have recently demonstrated a prolongation in mPFS with berzosertib in combination with gemcitabine versus gemcitabine alone in the overall intent-to-treat population (22.9 *v* 14.7 weeks, $p = .047$), which was mainly due to the benefit observed in a subgroup analysis of the patients stratified for platinum-free interval ≤3 months.[109] Berzosertib is currently being evaluated in a further, phase I study in triple combination with carboplatin and gemcitabine in recurrent, platinum-sensitive disease (Table 6).

Conclusions

The identification of new, effective combination regimens including chemotherapeutic agents, PARP inhibitors, angiogenesis inhibitors and/or other novel, targeted agents may provide therapeutic options that could prove beneficial for a substantial proportion of patients, particularly in the early lines of treatment for advanced disease. Accordingly, based on the findings reported from multiple phase III trials and recent FDA approvals, PARP inhibitors may become a new standard of care for maintenance treatment of newly diagnosed patients with advanced ovarian cancer. Validation of key biomarkers able to predict response to agents in each drug class may further result in improved drug selection at treatment initiation, maintenance phase, or switch to a new therapeutic option in case of tumor resistance and disease progression.

Chemotherapy-free regimens of potentially comparable or greater efficacy, based on various combinations of PARP inhibitors, PD-1/PD-L1 antibodies, and/or VEGFR inhibitors are being actively pursued to reduce the burden of toxicity associated with treatment. The eagerly awaited results from the ongoing phase II–III trials outlined in this review will provide evidence on the feasibility of these new therapeutic approaches and their potential to change the current standards of care for

advanced disease. Investigational agents with novel mechanisms of action (i.e. inhibition of key factors in the cell cycle, DNA repair and protein kinase pathways), designed to overcome the limitations imposed by primary and secondary tumor resistance to available therapies, also appear to be opening new, promising avenues for selective targeting of ovarian tumors in concert with other DNA-damaging or targeted agents and PD-1/PD-L1 immune-checkpoint inhibitors.

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